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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,573	07/17/2006	James B. Lorens	021044-004110US	4166

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,573	LORENS ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 19-24* is/are pending in the application.

4a) Of the above claim(s) *18-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 19-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 12/04/06 has been acknowledged.

Claims 1-17 and 19-24 are examined in this office action

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

Election/Restrictions

Applicant's election with traverse of Group II claims 1-17 and 19-24 (wherein the elected subject matter is a method for identifying a compound that modulates angiogenesis related to the polypeptide of SEQ ID NO:456, (SUSP-1) in the reply filed on 12/04/06 is acknowledged. The traversal is on the ground(s) that inventions of group I-VIII stem from a common concept and theory, and are thus related. The applicant argues that there is no serious burden to examine groups I-VIII together. However, this is found NOT persuasive. As stated in the earlier office action the method of identifying compounds that modulates angiogenesis by interacting with nucleic acid sequences have different modes of operation, functions and effects as compared to the identification of compounds that interacts with a protein. Furthermore the method of screening compound in-vitro is distinct form the method of modulating angiogenesis in a subject. In addition there is a serious search burden to examine all the nucleic acid sequences, polypeptides (as claimed), since each have different structure and function wherein the search of one would not lead to other. Furthermore a compound that modulates the activity of a particular polypeptide may not modulate the activity of other polypeptide, since each polypeptide as claimed have structure and function and therefore have different mode of operation and effect.

The requirement is still deemed proper and is therefore made FINAL.

Claims 18, 25-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/04/06.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 and 19-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The scope of invention as claimed encompasses the use of any variant of recombinant SUSP-1 polypeptide (*derived from any natural (i.e. organism) or non-natural source)* encoded nucleic acid sequence of SEQ ID NO:456. At best the specification teaches SUSP-1 (SEQ ID NO:456). Besides the recombinant polypeptide (SEQ ID NO:456) which is encoded by the nucleic acid sequence of SEQ ID NO:457 the specification as filed fails to disclose any variant of SUSP-1.

Applicant is referred to the guidelines for *Written Description Requirement* published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110. The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In analyzing whether the written description

requirement is met for the genus claim, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. conserve motifs or domains).

The specification fails to disclose representative number of species by structure and function encompassed by genus as claimed. Furthermore the genus as claimed encompasses structurally and functionally distinct members. Claiming all divergent species that achieve a result as contemplated by the application without defining the representative number of species by structure and function is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. "The written description requirement has several policy objectives. The essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." In re Barker, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. See Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1566, 43USPQ2d 1398, 1404 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998)." To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention as claimed is "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention (January 5, 2001 Fed.Reg., Vo.66, No. 4, pp. 1099-11).

Since the specification fails to disclose a representative number of SUSP-1 species defined by structure and function, it is not possible to envision the claimed composition. One cannot describe what one has not conceived. (See Fiddes v. Baird, 30 USP2d 1481 at 1483). Therefore, the lack of disclosure in the specification is not

deemed sufficient to reasonably convey to one skilled in the art that the applicants were in possessions of the huge genera recited in the claims at the time the application was filed. Furthermore the possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).*

In the instant case the SUSP-1 like polypeptide has been defined only by a statement of function that broadly encompasses a polypeptide that modulates angiogenesis, which conveyed no distinguishing information about the identity of the claimed genetic material, such as its relevant structural or physical characteristics. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of even a single member of this genus would not be representative of other nucleic acid constructs genus and is insufficient to support the claim.

Claims 1-17 and 19-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a compound

that modulates the expression of αVβ3 integrin by modulating the biological activity of SUSP-1 (SEQ ID NO:457) in endothelial cells, does not reasonably provide enablement for a method capable of identifying compounds that modulates angiogenesis in any cellular or non-cellular systems. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of Invention

The instant invention relates to method of identifying compounds that modulates angiogenesis via a polypeptide encoded by nucleic acid sequences of SEQ ID NO:456 that encodes SEQ ID NO:457 (SUSP-1).

Breadth of Claims and Guidance Provided in the Specification

i) The instant invention is drawn to a method identifying compounds that modulates angiogenesis by contacting the compound with any variant of recombinant polypeptide of SEQ ID NO: 457 and determining any and all effects. ii) The claims are further drawn to a method identifying compounds that modulates angiogenesis by contacting the compound with any variant of recombinant polypeptide of SEQ ID NO: 457 expressed in an eukaryotic cell. iii) In addition a claim is also drawn to method of identifying compounds that modulates the expression of αVβ3 integrin protein in an endothelial cell that comprises any variant of SEQ ID NO 457.

At best the specification teaches that the cell expressing GFP-SUSP-1 fusion protein exhibit lower level of αVβ3 expression as compared to control cells (spec. page 69, example-3). *The specfication further disclosed that the GFP-SUSP-1 screening hit did not affect proliferation when expressed in HUVEC (human umbilical vein endothelial cells), PASMC (pulmonary artery smooth muscle cells), and NHDF (normal human dermal fibroblasts).* (See, e.g., FIG. 12.) SUSP-1 mRNA was found to be expressed in a variety of cell lines. (See, e.g., FIG. 13.). However the specification as filed fails to establish that the SUSP-1 is capable of modulating the angiogenesis via modulating the proliferation of *HUVEC (human umbilical vein endothelial cells), PASMC (pulmonary artery smooth muscle cells), and NHDF (normal human dermal fibroblasts).*

State of Art and Predictability

The state of the art at the time of filing was such that the SUMO-specific protease 1 (SUSP1), a mammalian SENP/Ulp, localizes within the nucleoplasm. SUSP1 depletion within cell lines expressing enhanced green fluorescent protein (EGFP) fusions to individual SUMO paralogues caused redistribution of EGFP-SUMO2 and -SUMO3, particularly into promyelocytic leukemia (PML) bodies. Further analysis suggested that this change resulted primarily from a deficit of SUMO2/3-deconjugation activity. Furthermore, SUSP1 has a strong paralogue bias toward SUMO2/3 and that it acts preferentially on substrates containing three or more SUMO2/3 moieties. I has been suggested that the SUSP1 may play a specialized role in dismantling highly conjugated SUMO2 and -3 species that is critical for PML body maintenancen (see Mukhopadhyay et al J Cell Biol. 174(7):939-949, 2006) SUSP1 expressed in *Escherichia coli* cells efficiently released SUMO-1 from SUMO-1·β-galactosidase fusion but not from other ubiquitin-like protein fusions, including Smt3·β-galactosidase, suggesting its role in the generation of matured SUMO-1 specifically from its precursors. Interestingly, reproductive organs, such as testis, ovary, and prostate, contained much higher amounts of SUSP1 mRNA than colon and peripheral blood leukocyte, whereas other tissues, such as heart and spleen, had little or none. These results suggest that SUSP1 may play a role in the regulation of SUMO-1-mediated cellular processes particularly related to reproduction Kim et al, J Biol Chem. 275(19):14102-6, 2000).

Angiogenesis is an important process during normal physiology and pathologic conditions such as ischemic diseases, chronic inflammatory diseases, and tumor growth. The regulation of angiogenesis is complex and involves cascade of cellular and transcriptional events. Angiogenesis involves degradation of basement membrane, migration and proliferation of capillary EC cells and formation of three-dimensional capillary tubes. The net balance of pro and anti-angiogenic factors determine whether new blood vessels are formed or not (i.e. proangiogenic molecules such as the vascular endothelial cell growth factor, the fibroblast growth factors angiopoietins and inhibitors of angiogenesis such as platelet factor-4, angiostatin, endostatin, and vasostatin) see Carmeliet Nat Med. 9(6):653-60, 2003).

Therefore, considering the role of various cellular and transcriptional factors in the regulation of angiogenesis and limited amount of guidance provided in the specification as filed regarding the role of SUSP-1, it is unclear how one skilled in the art would practice the invention as claimed without further extensive and undue amount of experimentation especially in context of the regulation of angiogenesis.

In addition the specification fails to disclose a representative number of SUSP-1 species defined by both structure and function (supra). The applicant's disclosure does not enable one skilled in the art to practice the invention as claimed without further undue amount of experimentation, which requires the identification and characterization of any and all variants encoded by the nucleic acid sequences of SEQ ID NO:457 especially in context to the modulation of angiogenesis and/or $\alpha V\beta 3$ expression. It would require an undue amount of experimentation to make and use the variants of SEQ ID NO:457 as claimed, wherein in the scope of variant encompasses any addition, substitution or deletion at random over the entire length of SEQ ID NO:457. In instant case screening of any and all natural and/or non-natural variants of a gene product, wherein unknown numbers of amino acid sequences are added substituted and /or deleted is not considered routine. Making and testing a point mutation is significantly different from the making and testing an amino acid sequences wherein unknown amino acids are added, deleted and/or substituted. The number of possible scenario increase geometrically with increase in percent non-identity. Such making and testing is nothing more than an invitation to further experimentation, since the specification can not be relied on to teach how to make the variants as claimed. One has to engage in extensive making and testing in order to obtain variants that meet the requirements for the claimed functional activity. This is not considered routine in the art and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Furthermore it is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the

sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. This is further evident from applicants own assertion that the "modification of the conserved amino acid residues would be most likely to have detrimental effect on protein activity". Therefore it is highly unpredictable that SUSP-1 variants as claimed herein would have any role in the modulation of angiogenesis, especially in context with $\alpha V\beta 3$ expression. The applicant fails to disclose a single variant of SUSP-1 which is capable of interacting with $\alpha V\beta 3$ integrins that furhter leads to the modulation of angiogenesis in any all kinds of cells. Thus considering the role of various cellular and transcriptional factors in the regulation of angiogenesis, it is considered highly unpredictable that SEQ ID NO: 457 or any variant of SEQ ID NO: 457, would encode a protien that has the asserted angiogenic activity.

The disclosure "shall inform how to use, not how to find out how to use for themselves." See In re Gardner 475 F.2d 1389, 177 USPQ 396 (CCPA 1973). Therefore considering the applicant's disclosure in view the state of the art regarding angiogenesis and the variants of SEQ ID NO:457, it is unclear how one skilled in the art would envision that a compound that exert any physical or chemical effect on the SEQ ID NO:457-like polypeptide or any fragment thereof (in isolation or expressed on a cell) is also capable of modulating angiogenesis via any pathway. Furthermore the specification fails to provide any guidance how one skilled in the art would envision that any chemotaxis or hepatotaxis response initiated by the polypeptide of SEQ ID NO:457 or any variant of SEQ ID NO:457 that represent modulation of angiogenesis. For example considering the applicant's disclosure it is unclear that the SUMO-specific protease 1 (SUSP1), which plays a specialized role in dismantling highly conjugated SUMO2 and -3 species that is critical for PML body maintenance is also essential for the regulation of angiogenesis in any tissue.

The USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement

rejections are those raised in the art by artisans of expertise. Thus it would requires an undue amount of experimentation to establish that a compound that merely interacts with the polypeptide or any fragment thereof encoded by the nucleic acid sequence of SEQ ID NO:68 would modulate angiogenesis as claimed.

It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In instant case the examples provided in the instant specification are prophetic and read as instructions rather than examples, leaving significant amount of experimentation necessary to practice the invention.

In instant case regulation of angiogenesis by modulating the expression of SUSP-1(SEQ ID NO:457) or any variant thereof in any acellular or cellular assay is not considered routine in the art and without sufficient guidance to the role of SEQ ID NO:457 or any variant thereof in context of a specific assay used in the modulation of angiogenesis the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to practice the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 and 19-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "functional effect" sec. (ii). It is unclear what functional effect is determined in the context of invention as claimed.

Claim 3 recites "physical effect" in line 2. It is unclear what is the physical effect in the context of invention as claimed.

Claim 4 recites "measuring ligand or substrate binding" in line 2. It is unclear what ligand or substrate binding is measured in the context of invention as claimed.

Claim 5 recites "chemical effect" in line 2. It is unclear what is the chemical effect in the context of invention as claimed.

Claim 6 recites "measuring enzymatic activity" in line 2. It is unclear what enzymatic activity is measured in the context of invention as claimed.

Claim 8 recites "physical effect" in line 2. It is unclear what is the physical effect in the context of invention as claimed.

Claim 9 recites "measuring ligand or substrate binding" in line 2. It is unclear what ligand or substrate binding is measured in the context of invention as claimed.

Claim 5 recites "chemical or phenotypic effect" in line 2. It is unclear what are the chemical or phenotypic effects in the context of invention as claimed.

Claim 11 recites "measuring enzymatic activity" in line 2. It is unclear what enzymatic activity is measured in the context of invention as claimed.

Claim 24 recites "functional effect" in sec. (ii). It is unclear what functional effect is determined in the context of instant invention as claimed.

Claim 24 recites "phenotypic or chemical effect" in sec (iii). It is unclear what phenotypic or chemical effects are determined in the context of invention as claimed.

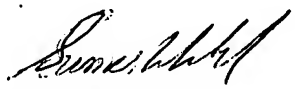
Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**



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